A specific mapping study using fluorescence sentinel lymph node detection in patients with intermediate- and high-risk prostate cancer undergoing extended pelvic lymph node dissection

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Abstract

Sentinel lymph node (SLN) detection techniques have the potential to change the standard of surgical care of patients with prostate cancer. We performed a lymphatic mapping study and determined the value of fluorescence SLN detection with indocyanine green (ICG) for the detection of lymph node metastases in intermediate- and high-risk patients undergoing radical prostatectomy and extended pelvic lymph node dissection. A total of 42 patients received systematic or specific ICG injections into the prostate base, the mid-portion, the apex, the left lobe or the right lobe. We found that: 1. external and internal iliac regions encompass the majority of SLNs; 2. common iliac regions contain up to 22% of all SLNs; 3. a prostatic lobe can drain into the contralateral group of pelvic lymph nodes; 4. the fossa of Marcille also receives significant drainage. Among the 12 patients who received systematic ICG injections, 5 (42%) had a total of 29 lymph node metastases. Of these, 16 nodes were ICG-positive, yielding 55% sensitivity. The complex drainage pattern of the prostate and the low sensitivity of ICG for the detection of lymph node metastases reported in our study highlight the difficulties related to the implementation of SNL techniques in prostate cancer.

Patient summary: There is controversy over how extensive lymph node dissection should be during prostatectomy. We investigated the lymphatic drainage of the prostate and whether sentinel node fluorescence techniques would be useful to detect node metastases. We found that the drainage pattern is complex and that the sentinel node technique is not able to replace extended pelvic lymph node dissection.

Main text

The role of pelvic lymph nodes dissection (PLND) during radical prostatectomy (RP) remains a matter of continuous debate (1). Sentinel lymph node (SLN) detection has been advanced as a potential alternative to PLND. In prostate cancer, the technique was first described using ^{99m}technetium bound to a colloid (2). However, radio-guided SLN detection has not come into widespread use. The use of the fluorescent dye indocyanine green (ICG) may open the door to a broader acceptance of SLN techniques in prostate cancer surgery (3). Against this background, we provide a comprehensive description of lymphatic landing sites per anatomical region of the prostate using this SLN technique. We also evaluate the sensitivity of ICG-based fluorescence SLN detection to detect lymph node metastases in intermediate- and high-risk patients.

Detailed information on patient selection and detection technique is found in Supplementary Patients and Methods. From November 2012 through September 2015, 42 patients presenting with clinically localized intermediate- or high-risk prostate cancer and scheduled for RP gave written informed consent to participate in our prospective study. ICG (Pulsion Medical Systems, Feldkirchen, Germany) was injected transrectally shortly prior to laparotomy. The first 12 patients enrolled received sextant injections (six injections into base, mid-portion, and apex of each prostatic lobe peripheral zone). The next 30 patients received injections into one of these sites: 1. prostate base bilaterally; 2. mid-portion bilaterally; 3. apex bilaterally; 4. left lobe (base, mid-portion, apex); or 5. right lobe (base, mid-portion, apex). A near-infrared-sensitive probe (Fluobeam®, Fluoptics, Grenoble, France) was used to collect fluorescence generated in the tissue under real-time image guidance. Independent of the findings of fluorescence SLN detection, an extended PLND was subsequently performed. An ex-vivo fluorescence examination of all dissected lymph nodes was then carried out. Lymphatic landing sites per anatomical region of the prostate were depicted graphically. Diagnostic statistics assessed the value of ICG in detecting lymph node metastases.

Baseline characteristics of the patients are summarized in Supplementary Table 1. All 42 patients had one or more lymph nodes detected by fluorescence. The lymphatic mapping study showed that (Fig. 1 and Supplementary Table 2): 1. the external and internal iliac regions encompass the majority of SLNs; 2. the common iliac regions contain up to 22% of all SLNs; 3. a prostatic lobe can drain into the contralateral group of pelvic lymph nodes; 4. the fossa of Marcille also receives significant drainage; and 5. practically all sites of the prostate can drain to different regions of the pelvis bilaterally.

Thus, the drainage pattern did not show that distinct lymphatic pathways exist per prostatic anatomical region. Our results also underscore crossover of lymphatics to the opposite side and that the common iliac regions and the fossa of Marcille should not be overlooked during PLND, as combined they may contain up to a third of all SLNs. The multitude of lymphatic landing sites as well as the individual variability of lymphatic drainage may represent an obstacle to intra-operative SLN detection. In contrast to breast cancer, in prostate cancer lymph node metastases do not follow a pre-defined pathway of metastatic spread and there is no certainty that the histologic status of the SLN reflects the status of the entire pelvic node basin.

Among the 12 patients who received systematic ICG injections a median of 15 SLNs per patient were removed (IQR 10-20). Five patients had a total of 29 lymph node metastases (Table 1). Of these, 16 were ICG-positive, yielding a sensitivity for the detection of lymph node metastases of 55%. The negative predictive value was 95%, the specificity was 57%, and the predictive positive value 8%. Repeating analyses with patients as unit of analysis showed that four of five patients had ICG-positive lymph node metastases, yielding a sensitivity for the correct staging of patients of 80%.

Hruby et al evaluated 38 patients who underwent laparoscopic RP (4). The sensitivity of the SLN technique with ICG to detect metastases was 98% (42 nodes in 15 patients). Yuen et al reported on 66 patients who underwent RP and SNL detection using ICG (5). Only nine metastases in six patients were detected, all of which were ICG-positive. Our median number of nodes removed was 35 vs. 18 in both previous reports. These findings suggest that our template leads to a notably more complete PLND, which would result in more precise sensitivity analyses. In addition, our median number of SLNs removed was 15 (IQR 10-20), which is in the higher range of most previous studies using ICG alone or in combination with a radio-colloid (3–6). Other authors may not have searched as thoroughly for SLNs in surgically less accessible regions such as the proximal part of the common iliac vessels, in the fossa of Marcille and in the presacral regions. In Yuen et al's study, only 2% and 1% of all SLNs were found in the common iliac and presacral regions, respectively (5).

The low sensitivity of ICG to detect metastases in the current study raises the concern of skip metastases. The presence of tumor cells in the lymph nodes may clog the feeding lymphatics and interfere with their ability to take up ICG, as it has been postulated for radio-colloids (7). Interestingly, we could sometimes visualize that lymphatic drainage goes around enlarged nodes. Going forward, emerging molecular imaging modalities using dyes conjugated with tumor-specific peptides may provide added sensitivity (8–10). It has to be noted that it is not possible to discriminate with certainty between primary landing sites and higher levels of drainage. However, the fact that fluorescent lymph nodes appeared 15-30 min after ICG injection and that direct drainage through lymphatic vessels could be seen in some cases suggests that these lymph nodes can be considered SLNs. Our study is limited by its small sample size. Nevertheless, it included a high number of lymph node metastases in the setting of extended PLND, allowing appropriate sensitivity analyses.

In conclusion, our lymphatic mapping study delineated a complex drainage pattern of the prostate that questions whether targeted lymph node dissection can be implemented in prostate cancer. Together with the low sensitivity for the detection of metastases, these results suggest that for the time being fluorescence SNL detection does not represent an alternative to a meticulously performed PLND in higher-risk patients.

Conflicts of interest: the Fluobeam® imaging device was provided at no charge by Fluoptics. However, the authors had complete control of the data and information submitted for publication.

Figure legend

Fig. 1. Percentages of sentinel nodes detected per drainage region with regard to anatomical sites of the prostate. The ICG injection sites are depicted in the upper right corner. The orange zones represent the external iliac regions, the yellow zones the internal iliac regions, the green zones the common iliac regions, and the regions delineated by dashed lines the fossas of Marcille.

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